

The Efficacy of Zinc Gluconate Supplementation in the Improvement of Malnutrition Indices and Skin Abnormalities in Hemodialysis Patients: A Randomized Clinical Trial

Abstract

Background: Hemodialysis patients often suffer from several complications such as malnutrition and skin abnormalities. We hypothesized that zinc supplementation may improve these complications. The aim of the present study was to examine the effects of zinc gluconate supplementation on malnutrition and skin abnormalities. **Methods:** In this parallel randomized, double-blind, clinical trial, patients in the zinc group received 210 mg zinc gluconate (equivalent to 30 mg elemental zinc) per day. Skin abnormalities (i.e. xerosis and pruritus), body composition, anthropometric variables, handgrip strength, and appetite (including hunger, fullness, desire to eat, and prospective food consumption) were measured at the beginning and end of the study. **Results:** Eighty-seven hemodialysis patients were randomly assigned to the zinc ($n = 44$) or placebo ($n = 43$) group for 12 weeks. After this period, 75 patients ($N = 38$ in the zinc group and 37 in the placebo group) remained in the study. In this study, no specific side effects of zinc supplementation were observed and twelve participants were lost to follow-up ($n = 6$ in each group) because of migration, kidney transplantation, death, dialysis access infection, and personal reasons. Zinc supplementation had beneficial effects on hunger) 95% CI: 9/55 (3/67-15/42)), desire to eat) 95% CI: 7/03 (1/82-12/24)), and prospective food consumption) 95% CI: 3/46 (0/3-14/1)) compared with placebo. Also, zinc improved pruritus) 95% CI: -0/52 (-0/82 to -0/22)). We observed no changes in body composition, anthropometric variables, handgrip strength, and xerosis in the zinc group compared with the placebo. **Conclusions:** This randomized clinical trial showed that zinc supplementation yielded beneficial effects on appetite and pruritus in hemodialysis patients.

Keywords: Appetite, body composition, handgrip strength, hemodialysis, randomized clinical trial, zinc

Introduction

Chronic kidney disease (CKD) is a global public health burden.^[1] It affects more than 10% of the general population worldwide.^[2] Community Verified iconThere is an impairment in renal function (e.g. excretion of nitrogenous compounds and regulation of electrolytes and blood pressure) in patients with CKD.^[3] The main causes of CKD are diabetes, high blood pressure, and kidney stones.^[3] The process of eliminating nitrogenous wastes and removing excess fluid in end-stage renal disease (ESRD) is called dialysis, including hemodialysis (HD) and peritoneal dialysis.^[4] HD is the most common form of renal replacement therapy, accounting for approximately 69% of all renal replacement therapies and 89% of all

types of dialysis.^[5] Nevertheless, HD is not as efficient as normal kidney function and HD patients suffer from several complications, such as malnutrition and skin abnormalities.^[4]

Malnutrition is one of the most common complications in patients with ESRD and 30-70% of HD patients have some degree of malnutrition.^[6,7] Body composition and handgrip strength (HGS) are two useful markers of malnutrition in HD patients.^[8,9] Changes in body composition, including muscle wasting, reduced lean body mass, and increased fat mass, were observed in patients undergoing HD.^[10] Evidence showed that body composition monitoring was an independent predictor of quality of life and survival in patients with ESRD.^[10,11] In addition to the body composition, HGS is an indicator of some adverse outcomes

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Mohammad Tavassoli, Shahrzad Shahidi¹, Gholamreza Askari, Naser Tavakoli², Cain C. T. Clark³, Mohammad Hossein Rouhani

Nutrition and Food Security Research Center and Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran, ¹Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, ²Department of Pharmaceutics, School of Pharmacy and Novel Drug Delivery Systems Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran, ³Centre for Intelligent Healthcare, Coventry University, Coventry, CV1 5FB, UK

Address for correspondence:

Dr. Mohammad Hossein Rouhani,
Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: sm_rouhani@nutr.mui.ac.ir

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such as malnutrition and mortality in HD patients.^[12,13] It can be used as a functional and nutritional test and The 2020 'KDOQI (Kidney Disease Outcomes Quality Initiative) Clinical Practice Guideline for Nutrition in CKD' recommends that muscle function should be assessed by HGS in adults with CKD 1-5D to detect protein-energy wasting.^[14] Nutritional intervention may have beneficial effects on body composition and HGS.^[15]

Lack of appetite in patients with ESRD is suggested as a cause of malnutrition.^[16] Evidence showed that loss of appetite was related to symptoms of behavioral disorders, increased levels of pro-inflammatory mediators, hospitalization, low quality of life, and decreased survival.^[17] Lack of appetite should be managed by appetite-stimulating medications and/or nutritional supplementation.^[18] Since several medications are not safe in patients with ESRD,^[19] nutritional supplementation may be a choice in managing loss of appetite in HD patients.^[19]

Skin abnormalities are common complications in HD patients.^[20] About 50-85% of patients undergoing HD suffer from skin abnormalities, such as xerosis cutis and pruritus.^[21,22] Also, skin discoloration has been observed in about 40% of HD patients.^[21,23] It seems that dietary intervention may improve skin abnormalities.^[24]

Zinc is an essential dietary trace element that acts as a coenzyme of several biochemical reactions and regulates gene expression, protein synthesis, immune function, and behavioral responses.^[25] Approximately 40-78% of patients undergoing HD suffer from zinc deficiency.^[26] Owing to the high prevalence of zinc deficiency among these patients, it seems that zinc supplementation may improve some complications, such as malnutrition and skin abnormalities, in patients with ESRD. A clinical trial showed that zinc supplementation could improve appetite in children with CKD.^[27] Also, it may increase food intake in adults with CKD.^[28] Zinc has favorable effects on body composition. It can stimulate myogenesis and muscle regeneration.^[29] There is an increment of muscle mass in growing children resulting from zinc supplementation.^[30] Zinc deficiency is considered an independent predictor of sarcopenia and muscle mass loss.^[31] Also, it is associated with reduced lean body mass and fat deposition.^[32] In addition to malnutrition, zinc may have a role in the management of skin abnormalities.^[33] It has been used in the treatment of skin infections (leishmaniasis, warts), inflammatory dermatosis (acne vulgaris, rosacea), pigment disorders (melasma), and neoplasms (basal cell carcinoma).^[33]

Although previous studies have examined the effect of zinc supplementation on malnutrition and skin abnormalities, there is little data regarding HD patients. Also, zinc has been predominantly used in the form of zinc sulfate in previous clinical trials and the effect of the more absorbable forms of zinc (i.e. zinc gluconate), with fewer gastrointestinal

side effects, has not been widely assessed.^[34,35] Therefore, the aim of the present study was to examine the effects of zinc supplementation, in the form of zinc gluconate, on appetite, body composition, HGS, and skin abnormalities in HD patients.

Methods

This study was designed as a parallel, double-blind, randomized clinical trial. The duration of the study was 12 weeks and the study was carried out from October 2020 to October 2021, in Isfahan, Iran. This study was ethically approved by The Research Council and Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran, and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran (Code: IR.MUI.RESEARCH.REC.1399.405). This randomized clinical trial was registered at IRCT.ir on October 05, 2020 (Registration number: IRCT20130903014551N7).

Patients were selected from two dialysis centers according to the inclusion and exclusion criteria. patients were included in the study if they were 1) on HD for at least 3 months; 2) dialyzed at least twice a week; and 3) >18 years old. Patients were excluded from the research if they were 1) smokers; 2) pregnant or lactating; 3) on enteral or parenteral feeding; 4) had a history of cancer or advanced liver disease; 5) took any drugs that could affect dependent variables of the study; and 6) were not on a specific diet, except for usual diets prescribed to the HD patients. The following reasons were considered for withdrawal: 1) kidney transplant or death; 2) low compliance with intervention (consuming <85% of supplements/placebo); and 3) undergoing peritoneal dialysis.

The following equation was used to estimate the required sample size: $n = 2 [(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times S^2] / \Delta^2$. In this study, α (the probability of a Type I error) was 0.05, and β (the probability of a Type 2 error) was 0.20. Therefore, $Z_{1-\alpha/2}$ was 1.96 and $Z_{1-\beta}$ was 0.85. Lean body mass (LBM) was considered the main variable in this study. According to previous studies, S^2 for LBM in HD patients was 0.8 kg.^[36] The minimum detectable difference in LBM between the two groups (Δ) was 0.53 kg.^[37] Therefore, the required sample size in each group was 35 (70 in total). We referred to two dialysis centers to select eligible participants. At first, medical records of all patients in each center were assessed based on the inclusion and exclusion criteria, and potential eligible participants were identified. Then, the aim, design, and other details of the study were explained to the identified patients. Some patients did not agree to participate in the present study. Therefore, 87 patients completed a written informed consent form and were included in the study. Also, a code number was assigned to each individual. Then, all codes were entered into the SPSS software version 20. We selected 50% of patients by using "Random sample of cases" command in the SPSS. Therefore, participants were randomly

allocated in a ratio of 1:1 to either the zinc or placebo group. No blocking was applied in the present study. The staff who ran random allocation had no role in outcome assessment. All investigators who evaluated HGS, body composition, and skin abnormalities, and the staff who ran the statistical analysis were blinded to the codes and zinc groups. Therefore, except for a staff who generated a randomization list and allocated patients, other staff, investigators, and participants were blinded. Patients in the zinc group received one tablet containing 210 mg zinc gluconate (equivalent to 30 mg elemental zinc) per day, produced by Dineh Company, Tehran, Iran, for 12 weeks. Patients in the placebo group received a tablet that contained 30 mg starch, and its color, appearance, smell, and taste were comparable to the zinc tablet. The placebo used in our study was prepared in the School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. Starch and lactose, the main ingredients of the mentioned placebo, were mixed to produce granules. Granules were passed through a sieve and mixed with lubricant to reduce the friction. Then they were injected into a tablet press machine. Participants in both groups were recommended to take the tablets after breakfast on non-dialysis days. In dialysis days, supplements should be used after the first post-dialysis meal. A list of following dietary recommendations for dialysis patients was provided for participants in both groups: 1) avoid consuming solid oils, fried foods, salty foods, high-fat dairy products, processed foods, and junk foods; 2) limit consuming sugar-sweetened beverages; 3) limit consuming high phosphorus food such as legumes, nuts, dairy products, and meats; and 4) limit high potassium foods such as banana, spinach, orange, dates, tomato, and potato.

A questionnaire including demographic information, medical history, and medications was completed for each patient. Demographic information was obtained by oral questions. Data regarding medical history, medications, and supplements used currently were collected by reviewing clinical records. Patients were monitored 2-3 times per week because they had scheduled dialysis sessions. In each visit, patients gave completed food records. A trained dietician asked several questions regarding dietary recommendations and checked patients' responses by food records. Also, we asked about the number of used supplements/placebo and retained empty packages of supplements/placebo. Therefore, they were visited and monitored weekly during dialysis sessions to assess compliance with the intervention. Patients received supplements (zinc or placebo) every 2 weeks and the empty packages were retained.

Measurement of indices of appetite

Appetite was evaluated in a fasted state in the morning at the beginning and end of the study using a visual analog scale (VAS) questionnaire. VAS is a measurement tool and

a method used to assess variables that cannot be directly measured (e.g., pain and appetite).^[38] This questionnaire had four domains including hunger, fullness, desire to eat, and prospective food consumption.^[39] A 100-mm horizontal line was determined for each domain. The lowest feeling was scored zero and the highest was marked as 100. The validity and reliability of this questionnaire in Iranian populations were deemed acceptable.^[40]

Assessment of body composition

In our study, body composition was measured by using the bioimpedance analysis method based on the principle that electrical conductivity is not the same through different tissues, including muscle mass and adipose tissue.^[41] Accordingly, we measured muscle mass, body fat (BF), and visceral fat (VF) by this method. For accurate results, body composition was measured after dialysis sessions,^[14] and patients were asked to not consume alcohol, caffeine, or diuretics.^[42,43]

Assessment of anthropometric variables

We measured dry weight, to the nearest 100 g, with participants minimally clothed and unshod (Seca, CA, USA). Dry weight was defined as the minimum tolerable post-dialysis weight when there were no signs or symptoms of hypovolemia or hypervolemia.^[34] Height was measured based on the standard protocol using a standard stadiometer. Body mass index (BMI) was calculated as dry weight in kilograms divided by the square of height in meters.^[44]

Assessment of handgrip strength

HGS was measured according to the Southampton method.^[45,46] We assessed HGS with the patients seated, and elbows held in a 90-degree position. The opposite hand of the dialysis access was used to measure HGS. Measurements were repeated three times, and the mean of all three measurements was used in statistical analysis. We used the SH5002 SAEHAN Spring Hand Dynamometer.

Assessment of skin abnormalities

Xerosis is the medical term for dry skin.^[47] It was assessed using an overall dry skin score.^[48] Scoring was performed by following scale method^[48]: zero (without xerosis), 1 (mild: faint roughness with dull appearance), 2 (moderate: slight roughness, and whitish appearance), and 3 (severe: advanced roughness, redness present, eczematous changes, and cracks). This method was valid and reliable.^[47] Pruritus, defined as itchy skin, was evaluated by assessing 16 body regions.^[49] Scoring was performed by following scale method^[49]: zero (without pruritus), ≤2 regions (mild: 1 point), 3–5 regions (moderate: 2 points), 6–10 regions (moderate to severe: 3 points), 11–13 regions (severe: 4 points), and 14–16 regions (very severe: 5 points). The validity of this method among patients with renal diseases was acceptable.^[50] Xerosis and pruritus were assessed by a trained staff and we did not use a dermatologist.

Assessment of dietary intake

HD patients were asked to complete two 3-day food records (two non-dialysis and one dialysis day) from the 1st to 12th week of the intervention. Food diaries were analyzed using Nutritionist IV software (First Databank, San Bruno, CA, USA) based on the USDA food composition database and extra data regarding Iranian foods.

Statistical analysis

To test the normal distribution of variables, kurtosis between -2 and $+2$ and skewness between -7 to $+7$ were considered acceptable.^[51,52] In this study, quantitative variables were reported as a mean and standard deviation; and qualitative variables were reported as percentages. Intragroup analysis was performed using paired *t*-tests, and intergroup analysis was performed using independent samples *t*-test and analysis of variance (ANOVA). To adjust for confounding variables (energy intake and baseline values), analysis of covariance (ANCOVA) was applied. The distribution of qualitative variables was compared between the two groups using the Chi-square test. For all statistical analyses, SPSS software version 20 was used to analyze the data, with a significance level of $P < 0.05$. Data were analyzed using a per-protocol method.

Result

Results of the normality test revealed that the kurtosis was between -2 and $+2$ and skewness was between -7 and $+7$ for all variables. Figure 1 depicts the CONSORT flow diagram. One hundred one patients were screened for eligibility. Fourteen patients did not meet inclusion and exclusion criteria or declined to participate. Therefore, a total of 87 patients were randomly assigned to the zinc ($n = 44$) or placebo ($n = 43$) groups. Twelve participants were lost to follow-up ($n = 6$ in each group) because of migration, kidney transplantation, death, dialysis access infection, and personal reasons. Therefore, the data of 75 patients ($n = 38$ in zinc and $n = 37$ in placebo groups) were analyzed.

General characteristics of HD patients enrolled in the present study are reported in Table 1. There were no significant differences in the leading causes of ESRD including hypertension ($P = 0.46$), diabetes ($P = 0.23$), and autosomal dominant polycystic kidney disease ($P = 0.99$) between the two groups. Also, age ($P = 0.55$), sex ($P = 0.80$), marital status ($P = 0.38$), dialysis vintage ($P = 0.29$), dialysis frequency ($P = 0.73$), and serum zinc level ($P = 0.92$) was not different between the two groups.

Table 2 shows the comparison of energy-adjusted dietary intake between the zinc and placebo groups during the study. Results revealed that the intakes of carbohydrates ($P = 0.07$), protein ($P = 0.27$), fat ($P = 0.68$), sodium ($P = 0.27$), vitamin E ($P = 0.10$),

Table 1: General characteristics of hemodialysis patients enrolled in the present study

Variable	Zinc (<i>n</i> =38)	Placebo (<i>n</i> =37)	<i>P</i>
Sex			
Male (%)	26 (%68.4)	24 (%64.9)	0.80 ^c
Female (%)	12 (%31.6)	13 (%35.1)	
Age (year)	49.23 (±15.35) ^a	51.21 (±13.76)	0.55 ^b
Marital status			
Married (%)	29 (%76.3)	26 (%70.3)	0.38 ^c
Single (%)	9 (%23.7)	11 (%29.7)	
Hypertension (%)	23 (%60.5)	26 (%70.3)	0.46 ^c
Diabetes (%)	11 (%28.9)	16 (%43.2)	0.23 ^c
Autosomal dominant polycystic kidney disease (%)	2.6	2.7	0.99 ^c
Dialysis vintage (month)	32.39 (±27.94) ^a	40.5 ±37.97	0.29 ^b
Dialysis frequency (session/week)	2.86 (±0.41) ^a	2.83 ±0.37	0.73 ^b
Serum zinc (mg/dl)	81.94 (±16.82) ^a	82.32±18.28	0.92 ^b

^aContinuous variables are expressed as mean) SD(. ^b*P* values resulted from independent samples *t*-test for quantitative variables. ^c*P* values resulted from Chi-square for qualitative variables: *n* (%).

Table 2: Energy-adjusted dietary intake of the study participants during the study^a

Variable	Zinc group (<i>n</i> =38)	Placebo group (<i>n</i> =37)	<i>P</i> ^b
Carbohydrate (g/day)	200.62 (±59.67)	171.36 (±73.70)	0.07
Protein (g/day)	62.1 (±18.37)	59.35 (±26.58)	0.27
Fat (g/day)	49.59 (±13.51)	46.59 (±15.49)	0.68
Sodium (mg/day)	1909.46 (±1625.69)	1632.21 (±984.66)	0.70
Vitamin E (mg/day)	9.28 (±4.41)	10 (±4.20)	0.10
Vitamin C (mg/day)	107.41 (±61.94)	82.73 (±67.05)	0.28
Vitamin B1 (mg/day)	1.26 (±0.32)	1.08 (±0.41)	0.05
Vitamin B2 (mg/day)	1.47 (±0.63)	1.16 (±0.63)	0.11
Potassium (mg/day)	3057.01 (±1434.78)	2513.76 (±1565.33)	0.39
Calcium (mg/day)	1068.48 (±581.83)	777.73 (±593.86)	0.10
Selenium (mg/day)	78.09 (±27.98)	73.59 (±31.62)	0.63
Zinc (mg/day)	9.27 (±3.55)	8.13 (±3.47)	0.64
Dietary fiber (g/day)	23.4 (±10.83)	20.7 (±14.10)	0.90
Phosphor (mg/day)	1067.07 (±322.49)	921.47 (±398.68)	0.26

^aVariables are expressed as mean) SD(. ^b*P* value was adjusted for total energy intake. ^b*P* values resulted from independent samples *t*-test.

vitamin C ($P = 0.28$), vitamin B1 ($P = 0.05$), vitamin B2 ($P = 0.11$), potassium ($P = 0.39$), calcium ($P = 0.10$), selenium ($P = 0.63$), zinc ($P = 0.64$), dietary fiber ($P = 0.90$), and phosphor ($P = 0.26$) were not different between two groups.

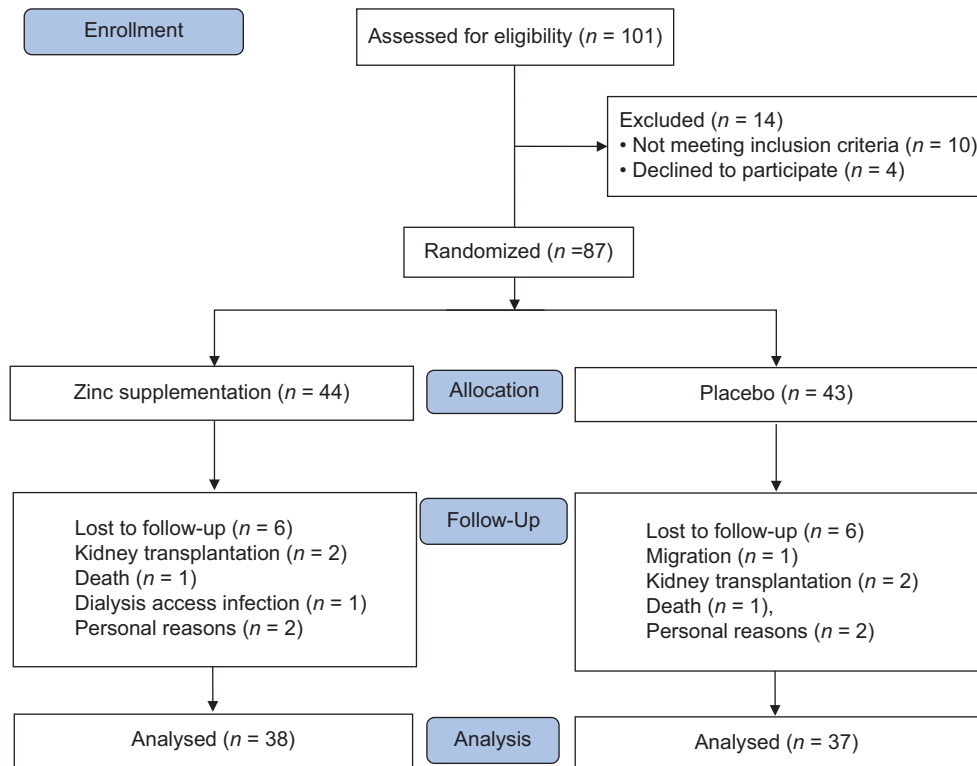


Figure 1: CONSORT flow diagram

The effects of zinc supplementation on hunger, prospective food consumption, fullness, and desire to eat in the intervention and placebo groups are shown in Figure 2. An improvement in hunger and desire to eat was observed after zinc supplementation compared with placebo. After adjusting for the baseline values, there were beneficial effects of zinc supplementation on hunger) 95% CI: 9/55 (3/67-15/42)), desire to eat) 95% CI: 7/03 (1/82-12/24)), and prospective food consumption (95% CI: 3/46 (0/3-14/1)) compared with a placebo. In contrast, zinc supplementation had no significant effect on fullness) 95% CI = -1/64 (-10/49 to 7/21)). The effects of zinc supplementation on dry weight) 95% CI = -0/7 (-3/22 to 1/81)), BMI) 95% CI: 0/27 (-0/14 to - 0/69)), BF, muscle mass) 95% CI: 0/8 (-0/6 to - 2/21)), VF, and HGS) 95% CI: 1/73 (-0/67 to 4/14)) are displayed in Table 3. After 12 weeks of intervention, results showed that dry weight, BMI, BF, VF, muscle mass, and HGS had no significant changes in zinc and placebo groups. Adjusting for baseline values did not change the results.

The effects of zinc supplementation on pruritus) 95% CI: -0/52 (-0/82 to - 0/22)) and xerosis score) 95% CI: -0/08 (-0/33 _0/16)) in the intervention and placebo group are shown in Table 4. In comparison with placebo, zinc supplementation elicited an improvement in pruritus. This finding was unchanged after adjusting for baseline measurements. There were no significant differences in xerosis between zinc and placebo groups before and after adjusting for baseline values.

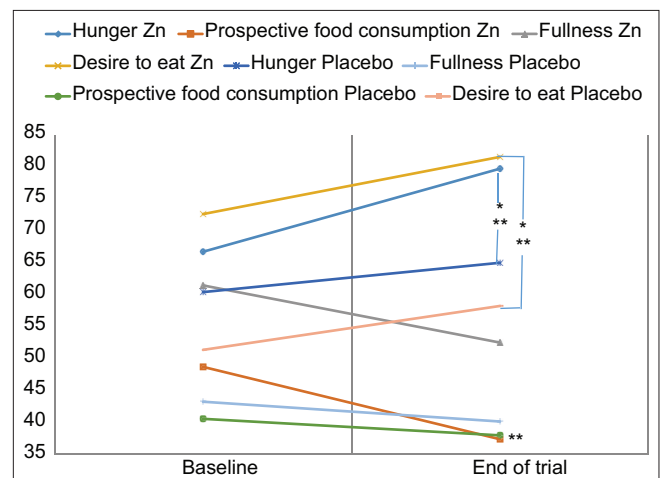


Figure 2: The effects of zinc supplementation on appetite indicators. *It shows significance ($P < 0.05$) in endpoint values between two groups obtained from independent t-test comparing endpoint measurements. **It shows significant ($P < 0.05$) final values between the two groups after adjusting for baseline measurements obtained from ANCOVA, adjusted for baseline value

Discussion

After 12 weeks of zinc gluconate supplementation, we observed that hunger, prospective food consumption, desire to eat, and pruritus were significantly improved compared with placebo. Malnutrition is one of the predominant predictors of a high rate of mortality in HD patients.^[53] Lack of appetite in patients with CKD is a potential cause of malnutrition and consequent mortality in

Table 3: The effects of zinc supplementation on body mass index, body composition, and handgrip strength

Variable	Zinc group (n=38)					Placebo group (n=37)				
	Baseline	End of trial	Change	P ^b		Baseline	End of trial	Change	P ^b	P ^c P ^d
Weight (kg)	68.31 (±16.65) ^a	67.41 (±19.42)	-0.90 (±7.23)	0.44		70.64 (±18.07)	70.53 (±18.22)	-0.10 (±2.6)	0.80	0.47 0.58
BMI (kg/m ²)	24.38 (±5.61)	24.41 (±5.57)	0.03 (±0.63)	0.73		25.38 (±5.98)	25.13 (±6.03)	-0.25 (±1.11)	0.18	0.59 0.19
BF (%)	26.27 (±11.08)	25.80 (±11.20)	-0.47 (±4.87)	0.55		25.02 (±13.44)	25.32 (±13.42)	0.29 (±2.89)	0.53	0.86 0.44
Muscle mass (%)	32.25 (±6.76)	32.86 (±6.71)	0.60 (±4.05)	0.36		33.7 (±6.32)	33.32 (±6.28)	-0.37 (±1.72)	0.19	0.75 0.26
VF (%)	8.23 (±6.01)	8.36 (±5.77)	0.13 (±1.25)	0.52		9.27 (±6.66)	9.18 (±6.59)	-0.08 (±1.18)	0.68	0.56 0.54
Handgrip Strength (kg)	20.16 (±8.47)	22.05 (±9.21)	1.88 (±6.36)	0.07		23.16 (±9.04)	22.91 (±9.08)	-0.24 (±3.78)	0.69	0.68 0.15

BMI: body mass index; BF: body fat; VF: visceral fat. ^a Variables are expressed as mean (SD). ^b Obtained from paired *t*-test comparing baseline and endpoint values. ^c Obtained from independent samples *t*-test comparing endpoint measurements. ^d Obtained from ANCOVA, adjusted for baseline value, and comparing endpoint values.

Table 4: The effects of zinc supplementation on skin abnormalities

	Zinc group (n=38)				Placebo group (n=37)					
	Baseline	End of trial	Change	<i>P</i> ^b	Baseline	End of trial	Change	<i>P</i> ^b	<i>P</i> ^c	<i>P</i> ^d
Pruritus score	1.21 (±1.23) ^a	0.39 (±0.71)	−0.81 (±1.00)	0.001	1.32 (±1.15)	0.97 (±0.98)	−0.35 (±0.78)	0.010	0.005	0.001
Xerosis score	0.78 (±0.84)	0.26 (±0.55)	−0.52 (±0.82)	0.001	0.56 (±0.92)	0.27 (±0.69)	−0.29 (±0.74)	0.020	0.960	0.502

^a Variables are expressed as mean (SD). ^b Obtained from paired *t*-test comparing baseline and endpoint values. ^c Obtained from independent samples *t*-test comparing endpoint measurements. ^d Obtained from ANCOVA, adjusted for baseline value, and comparing endpoint values.

HD patients.^[16] Therefore, increased appetite following zinc supplementation may have beneficial effects on survival rates in these patients.

Our findings showed that zinc gluconate supplementation improved hunger, prospective food consumption, and desire to eat. Although previous studies did not assess the effect of zinc supplementation on appetite among HD patients, changes in appetite after zinc supplementation have been examined in other patients. For instance, a clinical trial that enrolled 80 preschool children showed that using 10 mg/day of zinc for 12 weeks had positive effects on energy intake and improved anorexia nervosa.^[28,54] Also, 24 weeks of zinc supplementation in children aged 2-10 years resulted in an improvement in appetite and growth compared with placebo.^[55]

In our study, zinc supplementation had a beneficial effect on pruritus. This finding was corroborated by previous studies. For instance, a clinical trial that enrolled 19 HD patients with persistent pruritus showed that using 445 mg/day of zinc sulfate resulted in pruritus improvement among 53% of the participants.^[33] Also, there is a direct and significant relationship between zinc levels and the occurrence of skin disorders such as pruritus.^[56]

There are several mechanisms that might explain the improvement of hunger, prospective food consumption, and desire to eat after zinc supplementation. Zinc has a role in the regulation of hormones involved in appetite control, such as leptin. Leptin is an appetite-controlling hormone secreted by adipose tissue responsible for inhibiting food consumption and increasing energy expenditure.^[57,58] The levels of leptin are increased in patients with CKD as a result of diminished renal clearance rate. Previous studies showed that zinc supplementation decreased serum leptin levels in HD children.^[59] Additionally, low zinc serum

concentration is negatively associated with high leptin levels in HD patients,^[59] where elevated leptin levels may cause, or contribute to, a loss of appetite and malnutrition in patients with renal failure.^[59] On the other hand, zinc may regulate the production of appetite-related peptides including neuropeptide Y (NPY) and ghrelin.^[60] NPY is a transporter and modulator of catecholamines in peripheral, sympathetic, and cardiovascular control.^[61]

The beneficial effect of zinc on pruritus may be explained by the antihistamine properties of zinc. HD patients have high levels of serum histamine, which may be a cause of pruritus in these patients.^[62] Topical use of zinc is common to relieve symptoms of pruritus.^[62] Moreover, zinc prevents mast cell degranulation and subsequent histamine secretion.^[63] Therefore, pruritus may be improved resulting in decreased levels of histamine.

We found that zinc supplementation had no significant effect on anthropometric variables and body composition. It should be noted that BMI and BF were in the normal range at baseline in our study. The mean BMI was 24.38 kg/m² in the zinc group. However, the global mean BMI among adults aged 18-81 years was 25.8 kg/m².^[64] The patients in our study were not underweight or cachectic. Also, the mean BF of the patients was 26.27% in the zinc group, where the average BF in adults aged 18-70 years is 10-15% in men and 20-30% in women.^[65] Therefore, the BF among participants of our study was in the normal range. Also, zinc had no effect on anthropometric variables and body composition because baseline measurements were in the normal range and participants had no complications in this regard.

We did not use serum zinc concentration as a biomarker of compliance with zinc supplementation because of controversies regarding the effect of zinc supplementation on

serum zinc concentration in patients with ESRD. Although serum/plasma zinc is the most commonly used biomarker of zinc status in healthy populations, it is considered a flawed biomarker.^[66] Indeed, it is commonly used because there is no better biomarker.^[66] In patients with CKD, zinc supplementation is not effective in patients with high creatinine serum (>5.0 mg/dl) such as HD patients.^[67] Also, zinc supplementation could not increase serum zinc in children with CKD.^[27] Therefore, serum zinc may be not a good biomarker for evaluating compliance with zinc supplementation in studies that recruited patients with ESRD such as HD patients.

Limitations of the present study must be considered: 1) We used a simple randomization method supposed to lead to selection bias. The blocked randomization method is preferable and future studies should use this method rather than a simple randomization. 2) Although we employed validated tools to measure outcomes, some outcomes were self-reported such as indices of appetite. The validity of self-reported data is limited by a type of measurement error called responsible bias.^[68] Indeed, individuals may over-/underestimate outcomes or have a misunderstanding of what an outcome is.^[69] In this study, we measured appetite indices by self-reported data. Therefore, findings should be compared with other similar studies.

Conclusions

This randomized clinical trial showed that zinc supplementation had beneficial effects on prospective food consumption, desire to eat, and pruritus in HD patients. However, it had no significant effect on anthropometric variables in non-cachectic patients.

Ethics approval and consent to participate

This randomized clinical trial was registered at IRCT.ir on October 05, 2020 (Registration number: IRCT20130903014551N7). Also, all participants completed an informed consent form.

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Author contribution statement

S.S and N.T designed the study. M.H.R and M.T collected data. M.H.R analyzed data. M.H.R and M.T interpreted results. C.C.T.C and M.T wrote the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Apetrii M, Timofte D, Voroneanu L, Covic A. Nutrition in chronic kidney disease-The role of proteins and specific diets. *Nutrients* 2021;13:956.
2. Kovesdy CP. Epidemiology of chronic kidney disease: An update 2022. *Kidney Int Suppl* (2011) 2022;12:7-11.
3. Vadakedath S, Kandi V. Dialysis: A review of the mechanisms underlying complications in the management of chronic renal failure. *Cureus* 2017;9:e1603.
4. Hakim RM, Lazarus JM. Initiation of dialysis. *J Am Soc Nephrol* 1995;6:1319-28.
5. Bello AK, Okpechi IG, Osman MA, Cho Y, Htay H, Jha V, *et al.* Epidemiology of haemodialysis outcomes. *Nat Rev Nephrol* 2022;18:378-95.
6. Wright M, Jones C. Renal Association Clinical Practice Guideline on nutrition in CKD. *Nephron Clin Pract* 2011;118(Suppl 1):c153-64.
7. Aparicio M, Cano N, Chauveau P, Azar R, Canaud B, Flory A, *et al.* Nutritional status of haemodialysis patients: A French national cooperative study. French Study Group for Nutrition in Dialysis. *Nephrol Dial Transplant* 1999;14:1679-86.
8. Keane D, Gardiner C, Lindley E, Lines S, Woodrow G, Wright M. Changes in body composition in the two years after initiation of haemodialysis: A retrospective cohort study. *Nutrients* 2016;8:702.
9. Hasheminejad N, Namdari M, Mahmoodi MR, Bahrampour A, Azmandian J. Association of handgrip strength with malnutrition-inflammation score as an assessment of nutritional status in hemodialysis patients. *Iran J Kidney Dis* 2016;10:30-5.
10. Zhang H, Tao X, Shi L, Jiang N, Yang Y. Evaluation of body composition monitoring for assessment of nutritional status in hemodialysis patients. *Ren Fail* 2019;41:377-83.
11. Rosenberger J, Kissova V, Majernikova M, Strausova Z, Boldizar J. Body composition monitor assessing malnutrition in the hemodialysis population independently predicts mortality. *J Ren Nutr* 2014;24:172-6.
12. Hwang SH, Lee DH, Min J, Jeon JY. Handgrip strength as a predictor of all-cause mortality in patients with chronic kidney disease undergoing dialysis: A meta-analysis of prospective cohort studies. *J Ren Nutr* 2019;29:471-9.
13. Delanaye P, Quinonez K, Buckinx F, Krzesinski JM, Bruyere O. Hand grip strength measurement in haemodialysis patients: Before or after the session? *Clin Kidney J* 2018;11:555-8.
14. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, *et al.* KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis* 2020;76 (3 Suppl 1):S1-107.
15. Holmes CJ, Racette SB. The utility of body composition assessment in nutrition and clinical practice: An overview of current methodology. *Nutrients* 2021;13:2493.
16. Wolley MJ, Hutchison CA. Large uremic toxins: An unsolved problem in end-stage kidney disease. *Nephrol Dial Transplant* 2018;33(Suppl 3):iii6-11.
17. Lopes AA, Elder SJ, Ginsberg N, Andreucci VE, Cruz JM, Fukuhara S, *et al.* Lack of appetite in haemodialysis patients--associations with patient characteristics, indicators of nutritional status and outcomes in the international DOPPS. *Nephrol Dial Transplant* 2007;22:3538-46.
18. Nagaraj S. Loss of appetite in adult patients: Effectiveness and safety of an appetite stimulating medication in an open-label, investigator-initiated study in India. *J Nutr Metab* 2022;2022:2661912.

19. Whittaker CF, Miklich MA, Patel RS, Fink JC. Medication safety principles and practice in CKD. *Clin J Am Soc Nephrol* 2018;13:1738-46.
20. Blaha T, Nigwekar S, Combs S, Kaw U, Krishnappa V, Raina R. Dermatologic manifestations in end stage renal disease. *Hemodial Int* 2019;23:3-18.
21. Markova A, Lester J, Wang J, Robinson-Bostom L. Diagnosis of common dermatopathies in dialysis patients: A review and update. *Semin Dial* 2012;25:408-18.
22. Szepletowski JC, Balaskas E, Taube KM, Taberly A, Dupuy P, Uraemic Xerosis Working G. Quality of life in patients with uraemic xerosis and pruritus. *Acta Derm Venereol* 2011;91:313-7.
23. Attia EA, Hassan SI, Youssef NM. Cutaneous disorders in uremic patients on hemodialysis: An Egyptian case-controlled study. *Int J Dermatol* 2010;49:1024-30.
24. Katta R, Kramer MJ. Skin and diet: An update on the role of dietary change as a treatment strategy for skin disease. *Skin Therapy Lett* 2018;23:1-5.
25. Wang LJ, Wang MQ, Hu R, Yang Y, Huang YS, Xian SX, *et al.* Effect of zinc supplementation on maintenance hemodialysis patients: A systematic review and meta-analysis of 15 randomized controlled trials. *Biomed Res Int* 2017;2017:1024769.
26. Nakatani S, Mori K, Shoji T, Emoto M. Association of zinc deficiency with development of CVD events in patients with CKD. *Nutrients* 2021;13:1680.
27. Escobedo-Monge MF, Ayala-Macedo G, Sakihara G, Peralta S, Almaraz-Gomez A, Barrado E, *et al.* Effects of zinc supplementation on nutritional status in children with chronic kidney disease: A randomized trial. *Nutrients* 2019;11:2671.
28. Suzuki H, Asakawa A, Li JB, Tsai M, Amitani H, Ohinata K, *et al.* Zinc as an appetite stimulator-the possible role of zinc in the progression of diseases such as cachexia and sarcopenia. *Recent Pat Food Nutr Agric* 2011;3:226-31.
29. Hernandez-Camacho JD, Vicente-Garcia C, Parsons DS, Navas-Enamorado I. Zinc at the crossroads of exercise and proteostasis. *Redox Biol* 2020;35:101529.
30. Friis H, Ndhlovu P, Mduluzi T, Kaondera K, Sandstrom B, Michaelsen KF, *et al.* The impact of zinc supplementation on growth and body composition: A randomized, controlled trial among rural Zimbabwean schoolchildren. *Eur J Clin Nutr* 1997;51:38-45.
31. Nishikawa H, Enomoto H, Yoh K, Iwata Y, Sakai Y, Kishino K, *et al.* Serum zinc concentration and sarcopenia: A close linkage in chronic liver diseases. *J Clin Med* 2019;8:336.
32. Touloukian RJ, Spencer RP. Blood flow to the ileal remnant following massive intestinal resection. *Surg Forum* 1971;22:370-1.
33. Sanada S, Kuze M, Yoshida O. [Beneficial effect of zinc supplementation on pruritus in hemodialysis patients with special reference to changes in serum histamine levels]. *Hinyokika Kiyo* 1987;33:1955-60.
34. Agarwal R, Weir MR. Dry-weight: A concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients. *Clin J Am Soc Nephrol* 2010;5:1255-60.
35. Richard MJ, Ducros V, Foret M, Arnaud J, Coudray C, Fusselier M, *et al.* Reversal of selenium and zinc deficiencies in chronic hemodialysis patients by intravenous sodium selenite and zinc gluconate supplementation. Time-course of glutathione peroxidase repletion and lipid peroxidation decrease. *Biol Trace Elem Res* 1993;39:149-59.
36. Pupim LB, Heimbürger O, Qureshi AR, Ikizler TA, Stenvinkel P. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. *Kidney Int* 2005;68:2368-74.
37. Ten Haaf DSM, Eijssvogels TMH, Bongers C, Horstman AMH, Timmers S, de Groot L, *et al.* Protein supplementation improves lean body mass in physically active older adults: A randomized placebo-controlled trial. *J Cachexia Sarcopenia Muscle* 2019;10:298-310.
38. Gould D, Kelly D, Goldstone L, Gammon J. Examining the validity of pressure ulcer risk assessment scales: Developing and using illustrated patient simulations to collect the data. *J Clin Nurs* 2001;10:697-706.
39. Gibbons C, Hopkins M, Beaulieu K, Oustric P, Blundell JE. Issues in measuring and interpreting human appetite (satiety/satiation) and its contribution to obesity. *Curr Obes Rep* 2019;8:77-87.
40. Rahmani Ghobadi M, Rahmaninia F, Mirzaei B, Hedayati M. Effects of 8 weeks of aerobic training on Agouti-related peptide, appetite hormones and insulin resistance in overweight sedentary women. *Pars Jahrom Univ Med Sci* 2016;14:1-8.
41. Lustgarten MS, Fielding RA. Assessment of analytical methods used to measure changes in body composition in the elderly and recommendations for their use in phase II clinical trials. *J Nutr Health Aging* 2011;15:368-75.
42. Mahon AK, Flynn MG, Iglay HB, Stewart LK, Johnson CA, McFarlin BK, *et al.* Measurement of body composition changes with weight loss in postmenopausal women: Comparison of methods. *J Nutr Health Aging* 2007;11:203-13.
43. Verdich C, Barbe P, Petersen M, Grau K, Ward L, Macdonald I, *et al.* Changes in body composition during weight loss in obese subjects in the NUGENOB study: Comparison of bioelectrical impedance vs. dual-energy X-ray absorptiometry. *Diabetes Metab* 2011;37:222-9.
44. Casadei K, Kiel J. Anthropometric Measurement. StatPearls. Treasure Island (FL); 2021.
45. Sousa-Santos AR, Amaral TF. Differences in handgrip strength protocols to identify sarcopenia and frailty-A systematic review. *BMC Geriatr* 2017;17:238.
46. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, *et al.* A review of the measurement of grip strength in clinical and epidemiological studies: Towards a standardised approach. *Age Ageing* 2011;40:423-9.
47. Kang BC, Kim YE, Kim YJ, Chang MJ, Choi HD, Li K, *et al.* Optimizing EEMCO guidance for the assessment of dry skin (xerosis) for pharmacies. *Skin Res Technol* 2014;20:87-91.
48. Serup J. EEMCO guidance for the assessment of dry skin (xerosis) and ichthyosis: Clinical scoring systems. *Skin Res Technol* 1995;1:109-14.
49. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: A new measure of pruritus. *Br J Dermatol* 2010;162:587-93.
50. Yoosefinejad AK, Karjalainen F, Momennasab M, Jahromi SE. Reliability and validity of the Persian version of 5-D itching scale among patients with chronic kidney disease. *BMC Nephrol* 2021;22:16.
51. George D. SPSS for Windows Step by Step: A Simple Study Guide and Reference, 17.0 Update, 10/e. Pearson Education India; 2011.
52. Hair J, Black WC, Babin BJ, Anderson RE. Multivariate Data Analysis (7th ed.). Upper Saddle River, New Jersey: Pearson Educational International; 2010.
53. Stojanovic M, Stojanovic D, Stefanovic V. The impact of malnutrition on mortality in patients on maintenance hemodialysis in Serbia. *Artif Organs* 2008;32:398-405.

54. Khademian M, Farhangpajouh N, Shahsanaee A, Bahreynian M, Mirshamsi M, Kelishadi R. Effects of zinc supplementation on subscales of anorexia in children: A randomized controlled trial. *Pak J Med Sci* 2014;30:1213-7.
55. Chao HC, Chang YJ, Huang WL. Cut-off serum zinc concentration affecting the appetite, growth, and nutrition status of undernourished children supplemented with zinc. *Nutr Clin Pract* 2018;33:701-10.
56. Ogawa Y, Kinoshita M, Shimada S, Kawamura T. Zinc and skin disorders. *Nutrients* 2018;10:199.
57. Anshu K, Tanu A, Parshant C, Neena S, Sunita T, Payal M, *et al.* Plasma leptin levels and body mass index in North Indian subjects: Correlation with insulin resistance. *JARMS* 2013;5:59-62.
58. Daschner M, Tonshoff B, Blum WF, Englaro P, Wingen AM, Schaefer F, *et al.* Inappropriate elevation of serum leptin levels in children with chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. *J Am Soc Nephrol* 1998;9:1074-9.
59. El-Shazly AN, Ibrahim SA, El-Mashad GM, Sabry JH, Sherbini NS. Effect of zinc supplementation on body mass index and serum levels of zinc and leptin in pediatric hemodialysis patients. *Int J Nephrol Renovasc Dis* 2015;8:159-63.
60. Sun JY, Jing MY, Wang JF, Zi NT, Fu LJ, Lu MQ, *et al.* Effect of zinc on biochemical parameters and changes in related gene expression assessed by cDNA microarrays in pituitary of growing rats. *Nutrition* 2006;22:187-96.
61. Lundberg JM, Pernow J, Franco-Cereceda A, Rudehill A. Effects of antihypertensive drugs on sympathetic vascular control in relation to neuropeptide Y. *J Cardiovasc Pharmacol* 1987;10(Suppl 12):S51-68.
62. Najafabadi MM, Faghihi G, Emami A, Monghad M, Moeenzadeh F, Sharif N, *et al.* Zinc sulfate for relief of pruritus in patients on maintenance hemodialysis. *Ther Apher Dial* 2012;16:142-5.
63. Gupta M, Mahajan VK, Mehta KS, Chauhan PS. Zinc therapy in dermatology: A review. *Dermatol Res Pract* 2014;2014:709152.
64. Ofenheimer A, Breyer-Kohansal R, Hartl S, Burghuber OC, Krach F, Schrott A, *et al.* Reference values of body composition parameters and visceral adipose tissue (VAT) by DXA in adults aged 18-81 years-results from the LEAD cohort. *Eur J Clin Nutr* 2020;74:1181-91.
65. Shalini O, Budge H, Michael S. Adipocytes in Normal Tissue Biology. 2014. 10.1016/B978-0-12-386456-7.04408-7.
66. Moran VH, Stammers AL, Medina MW, Patel S, Dykes F, Souverein OW, *et al.* The relationship between zinc intake and serum/plasma zinc concentration in children: A systematic review and dose-response meta-analysis. *Nutrients* 2012;4:841-58.
67. Paun S, Tudosie M, Petris R, Macovei R. The effects of Zinc on human body, including on renal failure and renal transplantation. *J Med Life* 2012;5:137-40.
68. Zayet TMA, Ismail MA, Varathan KD, Noor RMD, Chua HN, Lee A, *et al.* Investigating transportation research based on social media analysis: A systematic mapping review. *Scientometrics* 2021;126:6383-421.
69. Rosenman R, Tennekoon V, Hill LG. Measuring bias in self-reported data. *Int J Behav Healthc Res* 2011;2:320-32.